MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis

MASK study group ; et al ; Bousquet, Jean ; Schünemann, Holger J ; Hellings, Peter W

DOI: https://doi.org/10.1016/j.jaci.2016.03.025

MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis

Jean Bousquet, MD,[a,b,c] Holger J. Schünemann, MD,[d] Peter W. Hellings, MD,[e] Sylvie Arnavielhe, PhD,[f] Claus Bachert, MD,[g] Anna Bedbrook, BSc,[b] Karl-Christian Bergmann, MD,[h] Sinthia Bosnic-Anticevich, PhD,[i] Jan Brozek, MD,[d] Moises Calderon, MD,[j] G. Walter Canonica, MD,[k] Thomas B. Casale, MD,[l] Niels H. Chavannes, MD,[m] Linda Cox, MD,[n] Henry Chrystyn, PhD,[o] Alvaro A. Cruz, MD,[p] Ronald Dahl, MD,[q] Giuseppe De Carlo, MD,[r] Pascal Demoly, MD,[s,t] Phillipe Devillier, MD,[u] Gérard Dray, PhD,[v] Monica Fletcher, MSc,[w] Wytske J. Fokkens, MD,[x] Joao Fonseca, MD,[y] Sandra N. Gonzalez-Diaz, MD,[z] Lawrence Grouse, MD,[aa] Thomas Keil, MD,[bb] Piotr Kuna, MD,[cc] Désirée Larenas-Linnemann, MD,[dd] Karin C. Lodrup Carlsen, MD,[ee] Eli O. Meltzer, MD,[ff] Jaoquim Mullol, MD,[gg] Antonella Muraro, MD,[hh] Robert N. Naclerio, MD,[ii] Susanna Palkonen, MD,[r] Nikolaos G. Papadopoulos, MD,[jj] Giovanni Passalacqua, MD,[k] David Price, MD,[kk] Dermot Ryan, MD,[ll] Boleslaw Samolinski, MD,[mm] Glenis K. Scadding, MD,[nn] Aziz Sheikh, MD,[oo] François Spertini, MD,[pp] Arunas Valiulis, MD,[qq] Erkka Valovirta, MD,[rr] Samantha Walker, PhD,[ss] Magnus Wickman, MD,[tt] Arzu Yorgancioglu, MD,[uu] Tari Haahtela, MD,[vv] and Torsten Zuberbier, MD,[h] on behalf of the MASK study group* *Montpellier, Paris, St-Quentin-en-Yvelines, and Alès, France; Hamilton, Ontario, Canada; Leuven, Ghent, and Brussels, Belgium; Berlin and Wuerzberg, Germany; Glebe, Australia; London, Cambridge, Warwick, Manchester, Aberdeen, and Edinburgh, United Kingdom; Genoa and Padua, Italy; Tampa and Davie, Fla; Bahia, Brazil; Leiden and Amsterdam, The Netherlands; Odense, Denmark; Porto, Portugal; Nuevo León and Mexico City, Mexico; Seattle, Wash; Lodz and Warsaw, Poland; Oslo, Norway; San Diego, Calif; Barcelona, Spain; Chicago, Ill; Athens, Greece; Vilnius, Lithuania; Turku, Finland; Stockholm, Sweden; Manisa, Turkey; and Lausanne, Switzerland*

The selection of pharmacotherapy for patients with allergic rhinitis (AR) depends on several factors, including age, prominent symptoms, symptom severity, control of AR, patient preferences, and cost. Allergen exposure and the resulting symptoms vary, and treatment adjustment is required. Clinical decision support systems (CDSSs) might be beneficial for the assessment of disease control. CDSSs should be based on the best evidence and algorithms to aid patients and health care professionals to jointly determine treatment and its step-up or step-down strategy depending on AR control. Contre les

From [a]University Hospital, Montpellier; [b]MACVIA-LR, Contre les MAladies Chroniques pour un VIeillissement Actif en Languedoc-Roussillon, European Innovation Partnership on Active and Healthy Ageing Reference Site, Montpellier; [c]INSERM, VIMA: Ageing and Chronic Diseases, Epidemiological and Public Health approaches, Paris, and Université Versailles St-Quentin-en-Yvelines; [d]the Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton; [e]the Laboratory of Clinical Immunology, Department of Microbiology and Immunology, KU Leuven; [f]Kyomed, Montpellier; [g]the Upper Airways Research Laboratory, ENT Department, Ghent University Hospital; [h]Allergy-Centre-Charité at the Department of Dermatology, Charité–Universitätsmedizin Berlin, and Secretary General of the Global Allergy and Asthma European Network (GA^{2}LEN); [i]the Woolcock Institute of Medical Research, University of Sydney and Sydney Local Health District, Glebe; [j]Imperial College London–National Heart and Lung Institute, Royal Brompton Hospital NHS, London; [k]the Allergy and Respiratory Diseases Clinic, DIMI, University of Genoa, IRCCS AOU San Martino-IST, Genoa; [l]the Division of Allergy/Immunology, University of South Florida, Tampa; [m]the Department of Public Health and Primary Care, Leiden University Medical Center; [n]the Department of Medicine, Nova Southeastern University, Davie; [o]RiRL, Cambridge; [p]ProAR–Nucleo de Excelencia em Asma, Federal University of Bahia, and GARD Executive Committee; [q]the Department of Dermatology and Allergy Centre, Odense University Hospital, Odense; [r]EFA European Federation of Allergy and Airways Diseases Patients' Associations, Brussels; [s]EPAR U707 INSERM, Paris and EPAR UMR-S UPMC, Paris VI, Paris; [t]the Department of Respiratory Diseases, Montpellier University Hospital; [u]Laboratoire de Pharmacologie Respiratoire UPRES EA220, Hôpital Foch, Suresnes Université Versailles Saint-Quentin; [v]Ecole des Mines, Alès; [w]Education for Health, Warwick; [x]the Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam; [y]the Center for Research in Health Technologies and Information Systems–CINTESIS, Universidade do Porto; the Allergy Unit, Instituto CUF Porto e Hospital CUF Porto; the Health Information and Decision Sciences Department–CIDES, Faculdade de Medicina, Universidade do Porto; Faculdade de Medicina da Universidade do Porto, Porto; [z]Universidad Autónoma de Nuevo León; [aa]the University of Washington School of Medicine, Faculty of the Department of Neurology, Seattle; [bb]the Institute of Social Medicine, Epidemiology and Health Economics, Charité–Universitätsmedizin Berlin, and the Institute for Clinical Epidemiology and Biometry, University of Wuerzburg; [cc]the Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz; [dd]Clínica de Alergia, Asma y Pediatría, Hospital Médica Sur, Mexico City; [ee]the Department of Paediatrics, Oslo University Hospital, Oslo, and the Faculty of Medicine, Institute of Clinical Medicine, University of Oslo; [ff]the Allergy and Asthma Medical Group and Research Center, San Diego; [gg]Unitat de Rinologia i Clínica de l'Olfacte, Servei d'ORL, Hospital Clínic, Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, Barcelona; [hh]Food Allergy Referral Centre Veneto Region, Department of Women and Child Health, Padua General University Hospital; [ii]the Section of Otolaryngology-Head and Neck Surgery, University of Chicago Medical Center and Pritzker School of Medicine, University of Chicago; [jj]the Center for Pediatrics and Child Health, Institute of Human Development, Royal Manchester Children's Hospital, University of Manchester, and the Allergy Department, 2nd Pediatric Clinic, Athens General Children's Hospital "P&A Kyriakou," University of Athens; [kk]the Academic Centre of Primary Care, University of Aberdeen, and Research in Real-Life, Cambridge; [ll]Honorary Clinical Research Fellow, Allergy and Respiratory Research Group, University of Edinburgh; [mm]the Department of Prevention of Envinronmental Hazards and Allergology, Medical University of Warsaw; [nn]Royal National TNE Hospital, University College London; [oo]the Allergy and Respiratory Research Group, Centre for Population Health Sciences, University of Edinburgh; [pp]Service d'Immunologie et Allergie, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne; [qq]Vilnius University Clinic of Children's Diseases, Vilnius; [rr]the Department of Lung Diseases and Clinical Allergology, University of Turku; [ss]Asthma UK, London; [tt]Sachs' Children's Hospital, Stockholm, and the Institute of Environmental Medicine, Karolinska Institutet, Stockholm; [uu]the Department of Pulmonology, Celal Bayar University Manisa, Turkey, and GARD Executive Committee; and [vv]Skin and Allergy Hospital, Helsinki University Hospital, Helsinki.

MAladies Chroniques pour un VIeillissement Actif en Languedoc-Roussillon (MACVIA-LR [fighting chronic diseases for active and healthy ageing]), one of the reference sites of the European Innovation Partnership on Active and Healthy Ageing, has initiated an allergy sentinel network (the MACVIA-ARIA Sentinel Network). A CDSS is currently being developed to optimize AR control. An algorithm developed by consensus is presented in this article. This algorithm should be confirmed by appropriate trials. (J Allergy Clin Immunol 2016;138:367-74.)

Key words: *Allergic rhinitis, conjunctivitis, Allergic Rhinitis and its Impact on Asthma, MACVIA-LR, information and communication technology, clinical decision support system*

Abbreviations used

AR:	Allergic rhinitis
CDSS:	Clinical decision support system
MACVIA-LR:	Contre les MAladies Chroniques pour un VIeillissement Actif en Languedoc-Roussillon
MASK:	MACVIA-ARIA Sentinel Network
MCID:	Minimal clinically important difference
QOL:	Quality of life
RQLQ:	Rhinoconjunctivitis Quality of Life Questionnaire
VAS:	Visual analog scale

The selection of pharmacotherapy for patients with allergic rhinitis (AR) depends on several factors, such as age, prominent symptoms, symptom severity, control of AR, patient preferences, availability of treatment, and cost.[1] With allergen exposure and the resulting symptoms varying daily, patients with AR would benefit from regular monitoring of their symptoms to facilitate treatment adjustment. Clinical decision support systems (CDSSs) might be beneficial for the accomplishment of this task by assessing disease control, such as in response to treatment.[2] A CDSS is a health information technology system designed to assist health care professionals and patients with clinical decision-making

*Working group members**: Werner Aberer, MD; Mitsuru Adachi, MD; Ioana Agache, MD; Cezmi Akdis, MD; Mubeccel Akdis, MD; Isabella Annesi-Maesano, MD; Ignacio J. Ansotegui, MD; Josep M. Anto, MD; S. Hasan Arshad, MD; Ilaria Baiardini, MD; Abay K.Baigenzhin, MD; Cristina Barbara, MD; Eric D. Bateman, MD; Bianca Beghé, MD; Elisabeth H. Bel, MD; Ali Ben Kheder, MD; Kazi S. Bennoor, MD; Michael Benson, MD; David Bernstein, MD; Bewick Michael, MD; Bieber Thomas, MD; Carsten Bindslev-Jensen, MD; Leif Bjermer, MD; Hubert Blain, MD; Attilio Boner, MD; Matteo Bonini, MD; Sergio Bonini, MD; Isabelle Bosse, MD; Jacques Bouchard, MD; Louis-Philippe Boulet, MD; Rodolphe A. Bourret, PhD; Philippe J. Bousquet, MD; Fulvio Braido, MD; Andrew H. Briggs, PhD; Christopher E. Brightling, MD; Roland Buhl, MD; Peter Burney, MD; Andrew Bush, MD; Fernando Caballero-Fonseca, MD; Davide P. Caimmi, MD; Paulo Camargos, MD; Thierry Camuzat; Kai-Hakon Carlsen, MD; Warner Carr, MD; Thomas B. Casale, MD; Alfonso Cepeda Sarabia, MD; Leda Chatzi, PhD; Yuzhi Chen, MD; Raphaël Chiron, MD; Ekaterine Chkhartishvili, MD; Alexander Chuchalin, MD; Georgio Ciprandi, MD; Ieva Cirule; Jaime Correia de Sousa, MD; David Costa, MD; George Crooks, MD; Adnan Custovic, MD; Sven-Erik Dahlen, MD; Ulf Darsow, MD; Frédéric De Blay, MD; Esteban De Manuel Keenoy, MD; Tony Dedeu, MD; Diana Deleanu, MD; Judah Denburg, MD; Alain Didier, MD; Anh-Tuan Dinh-Xuan, MD; Dejan Dokic, MD; Habib B. Douagui, MD; Ruta Dubakiene, MD; Stephen Durham, MD; Mark Dykewicz, MD; Yehia El-Gamal, MD; Regina Emuzyte, MD; Antje Fink-Wagner, PhD; Alessandro Fiocchi, MD; Francesco Forastiere, MD; Amiran Gamkrelidze, MD; Bilun Gemicioğlu, MD; Jose E. Gereda, MD; Roy Gerth van Wijk, MD; Maia Gotua, MD; Ineta Grisle, MD; M. Antonieta Guzmán, MD; Tari Haahtela, MD; Joachim Heinrich, PhD; Birthe Hellquist-Dahl, PhD; Friedrich Horak, MD; Peter H. Howarth, MD; Marc Humbert, MD; Michael Hyland, PhD; Juan-Carlos Ivancevich, MD; Edgardo J. Jares, MD; Sebastian L. Johnston, MD; Olivier Jonquet, MD; Guy Joos, MD; Ki-Suck Jung, MD; Jocelyne Just, MD; Marek Jutel, MD; Igor P. Kaidashev, MD; Musa Khaitov, MD; Omer Kalayci, MD; Fuat Kalyoncu, MD; Paul Keith, MD; Nikolai Khaltaev, MD; Jorg Kleine-Tebbe, MD; Ludger Klimek, MD; Bernard Koffi N'Goran, MD; Vitezlav Kolek, MD; Gerard H. Koppelman, MD; Marek Kowalski, MD; Inger Kull, PhD; Violeta Kvedariene, MD; Bart Lambrecht, MD; Susanne Lau, MD; Daniel Laune, PhD; Lan Le Thi Tuyet, MD; Jing Li, MD; Phillipe Lieberman, MD; Brian J. Lipworth, MD; Louis Renaud, MD; Yves Magard, MD; Antoine Magnan, MD; Bassam Mahboub, MD; Ivan Majer, MD; Mika Makela, MD; Peter J. Manning, MD; Mohamad R. Masjedi, MD; Marcus Maurer, MD; Sandra Mavale-Manuel, MD; Erik Melén, MD; Elisabete Melo-Gomes, MD; Jacques Mercier, MD; Hans Merk, MD; Neven Miculinic, MD; Florin Mihaltan, MD; Branislava Milenkovic, MD; Yousser Mohammad, MD; Mathieu Molimard, MD; Isabelle Momas, PhD; Anna Montilla-Santana, MD; Mario Morais-Almeida, MD; Ralph Mösges, MD; Rachel Nadif, PhD; Leyla Namazova-Baranova, MD; Hugo Neffen, MD; Kristof Nekam, MD; Angelos Neou, MD; Bodo Niggemann, MD; Dieudonné Nyembue, MD; Robyn O'Hehir, MD; Ken Ohta, MD; Yoshitaka Okamoto, MD; Kim Okubo, MD; Solange Ouedraogo, MD; Pier-Luigi Paggiaro, MD; Isabella Pali-Schöll, MD; Stephen Palmer, MSc; Petr Panzner, MD; Alberto Papi, MD; Hae-Sim Park, MD; Ian Pavord, MD; Ruby Pawankar, MD; Oliver Pfaar, MD; Robert Picard, PhD; Bernard Pigearias, MD; Isabelle Pin, MD; Davor Plavec, MD; Wolfgang Pohl, MD; Todor Popov, MD; Dirkje S. Postma, MD; Paul Potter, MD; Lars K. Poulsen, PhD; Klaus F. Rabe, MD; Filip Raciborski, PhD; Françoise Radier Pontal, MD; Sakari Reitamo, MD; Maria-Susana Repka-Ramirez, MD; Carlos Robalo-Cordeiro, MD; Graham Roberts, MD; Francisco Rodenas, PhD; Christine Rolland, MD; Miguel Roman Rodriguez, MD; Antonino Romano, MD; José Rosado-Pinto, MD; Nelson A. Rosario, MD; Larry Rosenwasser, MD; Menachem Rottem, MD; Mario Sanchez-Borges, MD; Joaquim Sastre-Dominguez, MD; Peter Schmid-Grendelmeier, MD; Eli Serrano, MD; F. Estelle R. Simons, MD; Juan-Carlos Sisul, MD; Ingebjorg Skrindo, MD; Henriette A. Smit, PhD; Dirceu Solé, MD; Talant Sooronbaev, MD; Otto Spranger; Rafael Stelmach, MD; Timo Strandberg, MD; Jordi Sunyer, MD; Carel Thijs, MD; Ana-Maria Todo-Bom, MD; Massimo Triggiani, MD; Rudolf Valenta, MD; Antonio L. Valero, MD; Marianne van Hage, MD; Olivier Vandenplas, MD; Giorgio Vezzani, MD; Pakit Vichyanond, MD; Giovanni Viegi, MD; Martin Wagenmann, MD; Ulrich Wahn, MD; Wang De Yun, MD; Denis Williams, PhD; John Wright, MD; Barbara P. Yawn, MD; Panayiotis Yiallouros, MD; Osman M. Yusuf, MD; Heather J. Zar, MD; Mario Zernotti, MD; Luo Zhang, MD; Nanshan Zhong, MD; Mihaela Zidarn, MD.

Disclosure of potential conflict of interest: J. Bousquet has received consulting fees from Actelion, Almirall, Meda, Merck, Merck Sharp Dohme, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach; has received fees for participation in review activities from Almirall, AstraZeneca, Chiesi, GlaxoSmithKline, Meda, Merck, Merck Sharp Dohme, Novartis, OM Pharma, Sanofi-Aventis, Schering-Plough, Takeda, Teva, and Uriach; has received lecture fees from Almirall, AstraZeneca, Chiesi, GlaxoSmithKline, Meda, Merck, Merck Sharp Dohme, Novartis, OM Pharma, Sanofi-Aventis, Schering-Plough, Takeda, Teva, and Uriach; and has received payment for development of educational presentations from Almirall, AstraZeneca, Chiesi, GlaxoSmithKline, Meda, Merck, Merck Sharp Dohme, Novartis, OM Pharma, Sanofi-Aventis, Schering-Plough, Takeda, Teva, and Uriach. K.-C. Bergmann has received lecture fees from Novartis. S. Bosnic-Anticevich is a member of the Teva Pharmaceuticals Devices International Key Experts Panel, has received research support from Research in Real Life, and has received lecture fees and payment for developing educational presentations from Teva and Mundipharma. G. W. Canonica is on the Board for and has received consultancy and lecture fees from ALK-Abelló, Allergopharma, Allergy Therapeutics, Anallergo, Hal, Lofarma, Stallergenes, and Thermo Fisher. T. B. Casale is Executive Vice President of the American Academy of Allergy, Asthma & Immunology (AAAAI). L. Cox has received consultancy fees from Genentech and Allergopharma; has received fees for participation in review activities from Circassia and Biomay; is on the ABAI Board; was on the AAAAI Board; and has received lecture fees from several regional, local, and state allergy meetings. A. A. Cruz is on the Meda Pharma Board, has received research support from GlaxoSmithKline, and has received lecture fees and travel support from Meda. R. Dahl has received lecture fees from Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, ALK-Abelló, Cipla, Novartis, Meda, and Chiesi. G. De Carlo has received research support from Sanofi Pasteur MSD, Boehringer Ingelheim International, ALK-Abelló, Almirall, Stallergenes France, Air Liquide Sante International, Novartis, GlaxoSmithKline, Mundipharma, and Chiesi. P. Demoly has received consultancy fees from ALK-Abelló, Circassia, Stallergenes, ThermoFisher Scientific, DBV, and Chiesi and has received lecture fees from Menarini, AstraZeneca, GlaxoSmithKline, Allergopharma, and MSD. P. Devillier is on the Meda Pharma Board; has received consultancy fees from Stallergenes, ALK-Abelló, and GlaxoSmithKline; has received lecture fees from Stallergenes and ALK-Abelló; has received payment for manuscript preparation from Stallergenes; and has received travel support from Stallergenes and Meda. M. Fletcher has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Napp, and Teva and has received lecture fees from AstraZeneca, Boehringer Ingelheim, Napp,

tasks. Knowledge-based CDSSs consist of 3 parts: the knowledge base, an inference engine, and a mechanism to communicate.[3,4] The knowledge base contains the rules and associations of compiled data. The inference engine combines the rules from the knowledge base with the patient's data. The communication mechanism allows the system to show the results to the user, as well as have input into the system. CDSSs should be based on the best evidence and algorithms to aid patients and health care professionals to jointly determine the treatment and its step-up or step-down strategy depending on AR control.[1] Thus CDSSs should help optimize treatment.

Contre les MAladies Chroniques pour un VIeillissement Actif en Languedoc-Roussillon (MACVIA-LR [fighting chronic diseases for active and healthy ageing], http://macvia.cr-languedocroussillon.fr) is one of the reference sites of the European Innovation Partnership on Active and Healthy Ageing.[5] It initiated the project Integrated Care Pathways for Airway diseases (AIRWAYS ICPs)[6] and the allergy sentinel network MACVIA-ARIA Sentinel NetworK (MASK).[2] A knowledge-based CDSS is currently being developed to optimize AR control. The communication mechanism of MASK uses interconnected tablets and cell phones.[7,8] The proposed algorithm of the MACVIA-CDSS is presented in this article.

CONTROL OF AR AND RHINOCONJUNCTIVITIS

In asthmatic patients, the treatment strategy is based on disease control and current treatment.[9-11] The variability in symptom control is challenging and necessitates careful monitoring, as well as the step up/step down of individualized therapeutic regimens over time. Both long- and short-term maintenance and reliever approaches have been proposed,[12] including the combination of an inhaled corticosteroid and fast-onset long-acting β-agonist inhaler as maintenance and reliever therapy.[13]

Novartis, and Teva. W. J. Fokkens has received research support from Meda and has received payment for developing a webcast on treatment of rhinitis for general practitioners. J. Fonseca is on the Boehringer Ingelheim and Novartis Boards; has received consultancy fees from Novartis; has received research support from Fundação Ciência e Tecnologia and Fundação Calouste Gulbenkian; has received lecture fees from AstraZeneca, Aerocrine, Menarini, GlaxoSmithKline, MSD, and Vitoria; and has received travel support from AstraZeneca and Novartis. T. Keil has received research support from the European Union projects MeDALL and iFAAM. P. Kuna has received lecture fees from Adamed, Allergopharma, Almirall, AstraZeneca, GlaxoSmithKline, Hal, Meda, Pfizer, Polpharma, Stallergenes, Lekam, and Bayer and has received lecture fees and is on the advisory board from Boehringer Ingelheim, Celon Pharma, Chiesi, FAES, MSD, Novartis, Polpharma, and Teva. D. Larenas-Linnemann has received consultancy fees from Boehringer Ingelheim, Meda, Pfizer, Mit Pharma, and Chiesi; has received research support from AstraZeneca, MSD, Novartis, Sanofi, UCB, GlaxoSmithKline, Pfizer, MEDA, TEVA, Senosiain, Carnot; has received lecture fees from AstraZeneca, MSD, Movartis, Sanofi, Pfizer, and Meda; has received payment for development of educational presentations from Glenmark; and has received travel support from ALK-Abelló. K. C. Lodrup Carlsen has received research and travel support from EU MedALL, is on the Sanofi advisory board, has received research support from National and regional public funding applications. E. O. Meltzer has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Church & Dwight, GlaxoSmithKline, Greer, Johnson & Johnson, Meda, Mylan, Regeneron/Sanofi, and Teva; is self-employed; has received lecture fees from Greer, Meda, Merck, Mylan, Takeda, and Teva; and has received payment for developing educational presentations from Glenmark. J. Mullol is on the boards for Uriach, Meda, FAES, ALK-Abelló, and Sanofi; has received research support from GlaxoSmithKline, Uriach, FAES, and Meda; and has received lecture fees from Uriach, Hartington Pharmaceuticals, Novartis, FAES, Menarini, MSD, Pierre-Fabre, and UCB. A. Muraro has received consultancy fees from Meda. R. N. Naclerio is on the Merck and Sanofi allergy advisory boards, has received consultancy fees from Teva, is employed by the University of Chicago, and has received research support from Meda. S. Palkonen is on the GlaxoSmithKline European Health Advisory Board; has received research support from Air Liquide Sante International, ALK-Abelló, Almirall, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Chiesi, Mundipharma, Sanofi-Pasteur, and Stallergenes; has received travel support from Novartis; and declares that she regularly has dialogue with the funding partners listed above, who give unrestricted educational grants to the patient organization, EFA, for which she works as a Director. N. Papadopoulos has received research support from GlaxoSmithKline, Nestle, and Merck; has received payment for developing educational presentations from Abbvie, Sanofi, Menarini, and Meda; has received consultancy fees from GlaxoSmithKline, Abbvie, Novartis, Menarini, Meda, and ALK-Abelló; and has received lecture fees from Allergopharma, Uriach, GlaxoSmithKline, Stallergenes, and MSD. D. Price is on the boards for Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva; has received consultancy fees from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, and Teva; has received research support from the UK National Health Service, British Lung Foundation, Aerocrine, AKL Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Meda, Merck, Mundipharma, Napp, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva, Zentiva; has received lecture fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, SkyePharma, Takeda, and Teva; has received payment for manuscript preparation from Mundipharma and Teva; has a patent with AKL Ltd; has received payment for developing educational presentations from GlaxoSmithKline and Novartis; has stock in AKL Ltd; has received travel support from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva; has received funding for patient enrolment or completion of research from Almirall, Chiesi, Teva, and Zentiva; has served as a peer reviewer for grant committees for the Medical Research Council, Efficacy and Mechanism Evaluation Programme, and HTA; and is 80% owner of Research in Real Life, which receives unrestricted funding for investigator-initiated studies from Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, and Zentiva. D. Ryan is on the Boards for Stallergenes and Uriach; has received consultancy fees from Meda; is employed by Optimum Patient Care and University of Edinburgh; has received lecture fees from Meda, Chiesi, Teva, AstraZeneca, and Boehringer Ingelheim; has received payment for developing educational presentation from Meda; and is Chairman of the European Academy of Allergy and Clinical Immunology (EAACI) Primary Care Interest Group. A. Valiulis is a board member without financial interest of the nonprofit organizations the European Academy of Paediatrics, European Paediatrc Association, European Confederation of Primary Care Paediatricians, Lithuanian Paediatric Society, and Lithuanian Paediatric Respiratory Society; has received research support from European Union Social Fund and Lithuanian Ministry of Health; has received travel support from the European Academy of Pediatrics; is Chairman of Executive Board of IPOKRaTES Lithuania Fund. E. Valovirta has received travel support from Stallergenes. M. Wickman has received research support and lecture fees from Thermo Fisher, has received consultancy fees from Thermo Fisher and Microtest Dx, and has received payment for developing educational presentations from Stallergenes. T. Zuberbier has received consultancy fees from Ansell, Bayer Schering, DST, FAES, Fujisawa, HAL, Henkel, Kryolan, Leti, Menarini, Merck, MSD, Novartis, Procter & Gamble, Ranbaxy, Sanofi-Aventis, Schering Plough, Stallergenes, Takeda, and UCB; is on the German Society for Allergy and Clinical Immunology Scientific Advisory Board; is head of the European Centre for Allergy Research Foundation; is a World Health Organization Initiative Allergic Rhinitis and its Impact on Asthma committee member; is a member of the World Allergy Organization Communications Council; and is Secretary General of the Global Allergy and Asthma European Network. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 30, 2015; revised February 5, 2016; accepted for publication March 15, 2016.

Available online April 23, 2016.

Corresponding author: Jean Bousquet, MD, CHRU Arnaud de Villeneuve, Département de Pneumologie, 371 Avenue du Doyen Gaston, Giraud, 34295 Montpellier Cedex 5, France. E-mail: jean.bousquet@orange.fr.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749

http://dx.doi.org/10.1016/j.jaci.2016.03.025

Box 1. Summary of recommendations for the treatment of AR and conjunctivitis used in the algorithm

- Oral or intranasal H_1-antihistamines are less effective than intranasal corticosteroids for the control of all rhinitis symptoms.[28-33]
- Leukotriene receptor antagonists are usually considered less effective than oral H_1-antihistamines.[30,34,35]
- Comparisons between oral and intranasal H_1-antihistamines differ between recommendations, and thus no definite conclusions have yet been reached.
- Combined intranasal fluticasone propionate and azelastine hydrochloride in a single device is more effective than monotherapy and is indicated for patients when monotherapy with either an intranasal H_1-antihistamine or glucocorticoid is considered inadequate.[1,34-37]
- Intranasal antihistamines and intranasal corticosteroids are effective for ocular symptoms, with no significant difference between them.[38,39] However, the combination of azelastine and fluticasone propionate was more effective than fluticasone propionate alone.[36,37]
- In most studies, combinations of oral antihistamines or leukotriene receptor antagonists and intranasal corticosteroids are in general not more effective than monotherapy with intranasal corticosteroids.[40,41]
- Intraocular H_1-antihistamines or cromones are effective for ocular symptoms.[42] The importance of decongestants is debatable.[30] However, the efficacy of treatment varies with individual patient response.
- In clinical practice, intranasal corticosteroids need a few days to be fully effective, whereas intranasal H_1-antihistamines or combined intranasal fluticasone and azelastine are rapidly effective.[43]
- All recommended medications are considered safe at the usual dosage. First-generation oral H_1-antihistamines are sedating and should be avoided.[44]
- Oral or nebulized corticosteroids can be helpful in patients with severe disease whose symptoms are uncontrolled by other treatment, although studies are lacking in patients with AR.[45]
- Further studies are needed in preschool children to make more firm recommendations possible, although recent studies show the efficacy of oral H_1-antihistamines.[46]

The symptoms of AR can cause considerable morbidity in physical and emotional comfort, as well as in functional capacity and quality of life (QOL). The control and severity of AR have been defined in a similar manner to asthma.[2,14,15] Measures of AR control include symptom scores, patients' self-administered visual analog scales (VASs), objective measures of nasal obstruction, a recent modification of the Allergic Rhinitis and its Impact on Asthma severity classification, and patients' reported outcomes, such as QOL or scores with several items.[16,17] However, the challenges of managing AR are increased by the fact that patients do not often recognize their AR symptoms or confuse them with those of asthma.[18] Therefore it is important for patients to be able to use an AR symptom scoring system that is simple to use and rapidly responsive to change.

As is the case for asthma, the best control of AR should be achieved as early as possible to (1) improve patient satisfaction and concordance to treatment and (2) reduce the consequences of AR, including symptoms, reduced QOL, and school and work absenteeism. Untreated AR can impair driving ability and put patients at risk.[19] The ultimate goal of AR control is to reduce the costs incurred by AR.[20-23]

A step-up/step-down approach to AR pharmacotherapy based on patient response might hold potential for optimal AR control and cost of treatment.[1] MASK has proposed that electronic daily monitoring with VASs might help patients achieve optimal control of AR symptoms.[2] Well-controlled AR is defined as a VAS score of 2 or less of 10. VAS cutoff values to step up or down treatment were proposed by comparison with pain VAS scores and step-up schemes or from the literature in the field of allergy (see the additional material in this article's Online Repository at www.jacionline.org).[24-26]

RECOMMENDATIONS FOR THE TREATMENT OF AR AND RHINOCONJUNCTIVITIS

The treatment of AR also requires the consideration of (1) the type (rhinitis, conjunctivitis, and/or asthma) and severity of symptoms, (2) the relative efficacy of the treatment, (3) the speed of onset of action of treatment, (4) current treatment, (5) historic response to treatment, (6) patient's preference, (7) interest to self-manage, and (8) resource use. Guidelines[27] and various statements by experts for AR pharmacotherapy usually propose the approach summarized in Box 1.[28-46]

Allergen immunotherapy appears to be as effective as pharmacotherapy[47,48] but is also regarded as a disease modifier intervention with the potential of altering the natural history of allergic diseases.[49,50] Nonpharmacologic interventions, such as nasal filters[51] or saline, have been found to be effective.

PATIENTS' VIEWS

Many patients with AR are not satisfied with their current treatment,[52-54] and this results in frequent nonadherence to therapy.[55,56] In some studies, most patients were satisfied with their treatment, but full control was rarely achieved.[54,57-59] Despite the vast availability of treatment options, most patients are "very interested" in finding a new medication,[56,60] and around 25% are "constantly" trying different medications to find one that "works."[56] Patients want more effective treatments that can control all their symptoms, including ocular ones,[61,62] and a more rapid onset of action.[63]

Some patients believe that their health care provider does not understand their allergy treatment needs or does not take their allergy symptoms seriously.[52] Many patients self-medicate with over-the-counter drugs for a long period of time and usually only consult a physician when their treatment is ineffective.[58] In one study, patients chose a step-down therapy to speed up the control of symptoms.[64]

A patient's individual preference for an oral or intranasal route treatment needs to be considered.[52,64,65] In addition, health care professionals need to inform the patient of the relative benefits and harms of each prescribed treatment to support their decision making.

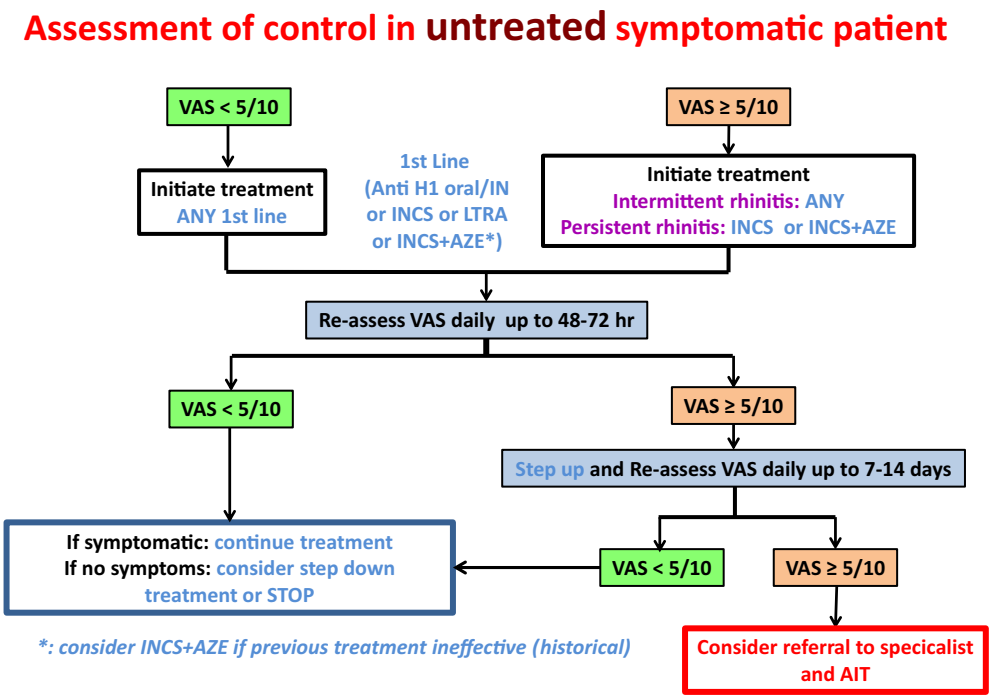

FIG 1. Step-up algorithm in untreated patients using the VAS (adolescents and adults). The proposed algorithm considers the treatment steps and patient preference and VAS levels in ratio. If ocular symptoms remain, add intraocular treatment.

ALGORITHM DECISION AID

A step-up/step-down individualized approach to AR pharmacotherapy might hold the potential for optimal control of AR symptoms while minimizing side effects and costs.[1] However, the following should be considered:

- as in asthmatic patients, treated and untreated patients should be considered differently (Figs 1 and 2);
- most patients have received a previous treatment that should guide health care professionals with regard to the current prescription; and
- patterns of medication use in previously treated patients should be evaluated when future treatment is initiated.

The step-up or step-down strategy should be discussed with the patient and should consider the following:

- efficacy of previous treatments;
- adherence to treatment;
- the patient's preference (route of administration, fear of side effects, and experience of the patient regarding the treatment);
- possible side effects or harms; and
- costs.

The step-up approach consists of the following:

- *Step 1*: For mild symptoms, use intranasal or oral nonsedating H_1-antihistamines.
- *Step 2*: For moderate-to-severe symptoms and/or persistent AR, use intranasal corticosteroids. The dose of some intranasal corticosteroids can be increased according to the package insert.
- *Step 3*: For patients with uncontrolled symptoms at step 2 (current or historical), use a combination of intranasal corticosteroids and intranasal H_1-antihistamines. However, depending on the physicians's experience, other therapeutic strategies can be used.
- *Step 4*: It is possible that an additional short course of oral steroids might help to establish control and continue control by step 3. Intraocular cromones or H_1-antihistamines can be added to improve the control of ocular symptoms.
- Treatment should be reassessed quickly (eg, 1-7 days) to confirm control by using a step-up approach.
- Patients whose symptoms are uncontrolled at step 3 should be considered as having severe chronic upper airway disease[66,67] and might benefit from specialist referral and assessment for allergy workup and nasal examination.[68] For example, specialist referral should be considered if there is failure to reduce the VAS score to less than 5 of 10 after 10 to 14 days, assuming the patient is adherent to therapy.
- At all times, patient adherence and intranasal device technique mastery should be regarded as potential for lack of treatment effect.

Alternatively, a step-down approach can be used, and step 3 treatment should be considered as the first option in patients with a previous treatment failure or resistance to monotherapy. After a few days of achieving complete control, consideration could be given to treatment reduction. However, the step-down approach is based on consensus, and more data are needed.

The duration of treatment is determined by the type of rhinitis (intermittent or persistent). In the patient with intermittent rhinitis, treatment should be continued daily for 2 weeks or for the duration of the pollen season or other specific allergen exposure. In the patient with persistent rhinitis, a longer course

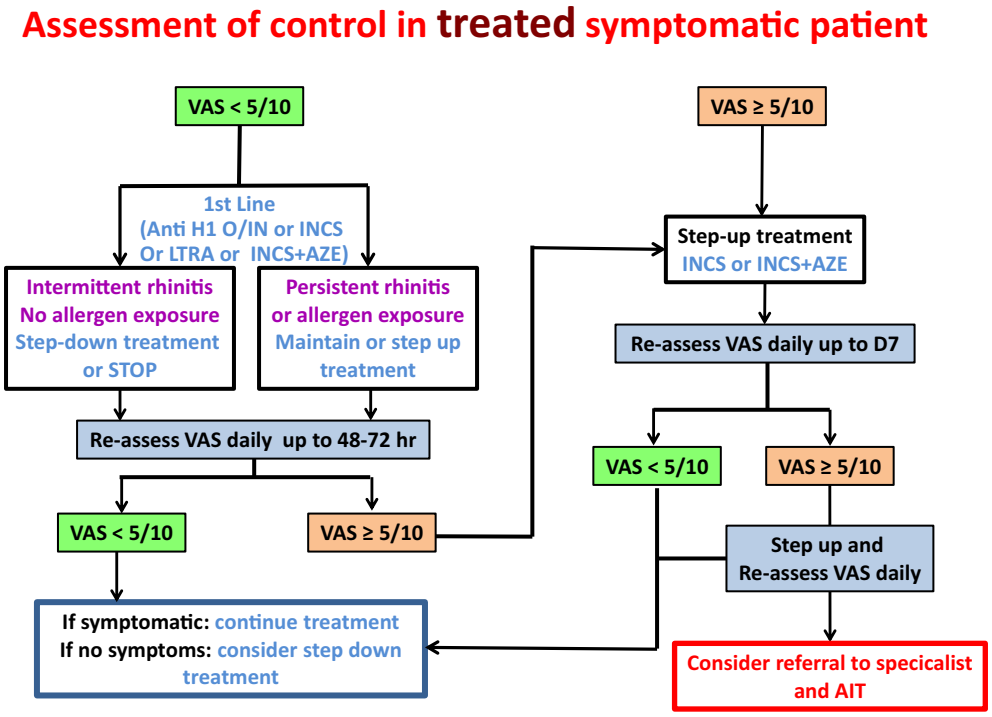

FIG 2. Step-up algorithm in treated patients using the VAS (adolescents and adults). The proposed algorithm considers the treatment steps and patient preference and VAS levels in ratio. If ocular symptoms remain, add intraocular treatment.

of treatment is often needed. Of course, it is important to assess concordance with agreed regimens because treatment failure can be a result of poor patient concordance.

CONCLUSION

We propose a simple algorithm to step up or step down AR treatment globally. However, its use varies depending on the availability of medications in different countries and depending on resources. These issues have not been approached in the present article because of their variability between countries. Inherently, algorithms are a combination of individual decision nodes that represent separate recommendations. They require testing as a complete algorithm and comparison with alternative strategies to explore whether the combination of these separate recommendations leads to more benefit than harm when applied in practice. Thus this algorithm, as with other algorithms, requires testing in large-scale trials to provide the necessary certainty in available evidence. The current algorithm is being developed by MASK[2] for a CDSS that will be available on Apple and Android and that will provide opportunities for evaluation.

REFERENCES

1. Meltzer EO. Pharmacotherapeutic strategies for allergic rhinitis: matching treatment to symptoms, disease progression, and associated conditions. Allergy Asthma Proc 2013;34:301-11.
2. Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW, et al. MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): the new generation guideline implementation. Allergy 2015;70:1372-92.
3. Berlin A, Sorani M, Sim I. A taxonomic description of computer-based clinical decision support systems. J Biomed Inform 2006;39:656-67.
4. Berner E. Clinical decision support systems: State of the Art. Rockville (MD): Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services; 2009.
5. Bourret R, Bousquet J. An integrated approach to telemonitoring noncommunicable diseases: best practice from the European innovation partnership on active and healthy ageing. World Hosp Health Serv 2013;49:25-8.
6. Bousquet J, Barbara C, Bateman E, Bel E, Bewick M, Chavannes N, et al. AIRWAYS ICPs (European Innovation Partnership on Active and Healthy Ageing) from concept to implementation. Eur Respir J 2016;47:1028-33.
7. Bousquet J, Hajjam J, Piette F, Jean-Bart B, Wlosik C, Robine JM, et al. [The French reference sites of the European Innovation Partnership on active and healthy ageing]. Presse Med 2013;42:1558-61.
8. Bousquet J, Addis A, Adcock I, Agache I, Agusti A, Alonso A, et al. Integrated care pathways for airway diseases (AIRWAYS-ICPs). Eur Respir J 2014;44:304-23.
9. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. J Allergy Clin Immunol 2007;120(suppl):S94-138.
10. O'Byrne PM, Reddel HK, Eriksson G, Ostlund O, Peterson S, Sears MR, et al. Measuring asthma control: a comparison of three classification systems. Eur Respir J 2010;36:269-76.
11. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J 2015;46:622-39.
12. Thomas A, Lemanske RF Jr, Jackson DJ. Approaches to stepping up and stepping down care in asthmatic patients. J Allergy Clin Immunol 2011;128:915-26.
13. Patel M, Pilcher J, Beasley R. Combination ICS/fast-onset LABA inhaler as maintenance and reliever therapy: the future for uncontrolled adult asthma? Expert Rev Respir Med 2013;7:451-4.
14. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol 2010;126:926-38.
15. WHO Collaborating Center for Asthma and Rhinitis, Bousquet J, Anto JM, Demoly P, Schunemann HJ, Togias A, Akdis M, et al. Severe chronic allergic (and related) diseases: a uniform approach—a MeDALL—GA2LEN—ARIA position paper. Int Arch Allergy Immunol 2012;158:216-31.
16. Schatz M, Meltzer EO, Nathan R, Derebery MJ, Mintz M, Stanford RH, et al. Psychometric validation of the rhinitis control assessment test: a brief patient-completed instrument for evaluating rhinitis symptom control. Ann Allergy Asthma Immunol 2010;104:118-24.

17. Demoly P, Jankowski R, Chassany O, Bessah Y, Allaert FA. Validation of a self-questionnaire for assessing the control of allergic rhinitis. Clin Exp Allergy 2011; 41:860-8.
18. Nolte H, Nepper-Christensen S, Backer V. Unawareness and undertreatment of asthma and allergic rhinitis in a general population. Respir Med 2006;100: 354-62.
19. Vuurman EF, Vuurman LL, Lutgens I, Kremer B. Allergic rhinitis is a risk factor for traffic safety. Allergy 2014;69:906-12.
20. Hellgren J, Cervin A, Nordling S, Bergman A, Cardell LO. Allergic rhinitis and the common cold—high cost to society. Allergy 2010;65:776-83.
21. Zuberbier T, Lotvall J, Simoens S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. Allergy 2014;69:1275-9.
22. Lamb CE, Ratner PH, Johnson CE, Ambegaonkar AJ, Joshi AV, Day D, et al. Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective. Curr Med Res Opin 2006;22:1203-10.
23. Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. J Allergy Clin Immunol 2007;120:381-7.
24. Bousquet PJ, Bachert C, Canonica GW, Casale TB, Mullol J, Klossek JM, et al. Uncontrolled allergic rhinitis during treatment and its impact on quality of life: a cluster randomized trial. J Allergy Clin Immunol 2010;126:666-8, e1-5.
25. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. Clin Exp Allergy 2013;43:881-8.
26. Ohta K, Jean Bousquet P, Akiyama K, Adachi M, Ichinose M, Ebisawa M, et al. Visual analog scale as a predictor of GINA-defined asthma control. The SACRA study in Japan. J Asthma 2013;50:514-21.
27. Padjas A, Kehar R, Aleem S, Mejza F, Bousquet J, Schunemann HJ, et al. Methodological rigor and reporting of clinical practice guidelines in patients with allergic rhinitis: QuGAR study. J Allergy Clin Immunol 2014;133: 777-83.e4.
28. Scadding GK, Durham SR, Mirakian R, Jones NS, Leech SC, Farooque S, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. Clin Exp Allergy 2008;38:19-42.
29. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122(suppl):S1-84.
30. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126:466-76.
31. Roberts G, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. Allergy 2013;68:1102-16.
32. Scadding GK. Optimal management of allergic rhinitis. Arch Dis Child 2015;100: 576-82.
33. Larenas-Linnemann D, Mayorga-Butron JL, Sanchez-Gonzalez A, Ramirez-Garcia A, Medina-Avalos M, Figueroa-Morales MA, et al. [ARIA Mexico 2014. Adaptation of the Clinical Practice Guide ARIA 2010 for Mexico. Methodology ADAPTE]. Rev Alerg Mex 2014;61(suppl 1):S3-116.
34. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice guideline: allergic rhinitis executive summary. Otolaryngol Head Neck Surg 2015;152:197-206.
35. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice guideline: allergic rhinitis. Otolaryngol Head Neck Surg 2015; 152(suppl):S1-43.
36. Hampel FC, Ratner PH, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol 2010;105:168-73.
37. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol 2012;129:1282-9.e10.
38. Fokkens WJ, Jogi R, Reinartz S, Sidorenko I, Sitkauskiene B, van Oene C, et al. Once daily fluticasone furoate nasal spray is effective in seasonal allergic rhinitis caused by grass pollen. Allergy 2007;62:1078-84.
39. Bielory L, Chun Y, Bielory BP, Canonica GW. Impact of mometasone furoate nasal spray on individual ocular symptoms of allergic rhinitis: a meta-analysis. Allergy 2011;66:686-93.
40. Anolik R. Mometasone Furoate Nasal Spray With Loratadine Study Group. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2008;100:264-71.
41. Esteitie R, deTineo M, Naclerio RM, Baroody FM. Effect of the addition of montelukast to fluticasone propionate for the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol 2010;105:155-61.
42. Castillo M, Scott NW, Mustafa MZ, Mustafa MS, Azuara-Blanco A. Topical antihistamines and mast cell stabilisers for treating seasonal and perennial allergic conjunctivitis. Cochrane Database Syst Rev 2015;6:CD009566.
43. Meltzer E, Ratner P, Bachert C, Carr W, Berger W, Canonica GW, et al. Clinically relevant effect of a new intranasal therapy (MP29-02) in allergic rhinitis assessed by responder analysis. Int Arch Allergy Immunol 2013;161:369-77.
44. Church MK, Maurer M, Simons FE, Bindslev-Jensen C, van Cauwenberge P, Bousquet J, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. Allergy 2010;65:459-66.
45. Wang C, Lou H, Wang X, Wang Y, Fan E, Li Y, et al. Effect of budesonide transnasal nebulization in patients with eosinophilic chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2015;135:922-9.e6.
46. Mullol J, Bousquet J, Bachert C, Canonica GW, Gimenez-Arnau A, Kowalski ML, et al. Update on rupatadine in the management of allergic disorders. Allergy 2015;70(suppl 100):1-24.
47. Matricardi PM, Kuna P, Panetta V, Wahn U, Narkus A. Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses. J Allergy Clin Immunol 2011;128:791-9.e6.
48. Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Med 2014;12:71.
49. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. J Allergy Clin Immunol 2015;136: 556-68.
50. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2016;137:444-51.e8.
51. Kenney P, Hilberg O, Pedersen H, Nielsen OB, Sigsgaard T. Nasal filters for the treatment of allergic rhinitis: a randomized, double-blind, placebo-controlled crossover clinical trial. J Allergy Clin Immunol 2014;133:1477-80, e1-13.
52. Marple BF, Fornadley JA, Patel AA, Fineman SM, Fromer L, Krouse JH, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. Otolaryngol Head Neck Surg 2007; 136(suppl):S107-24.
53. Ciprandi G, Incorvaia C, Scurati S, Puccinelli P, Soffia S, Frati F, et al. Patient-related factors in rhinitis and asthma: the satisfaction with allergy treatment survey. Curr Med Res Opin 2011;27:1005-11.
54. Frati F, Dell'Albani I, Passalacqua G, Bonini S, Rossi O, Senna G, et al. A survey of clinical features of allergic rhinitis in adults. Med Sci Monit 2014;20:2151-6.
55. Turner RR, Testa MA, Hayes JF, Su M. Validation of the allergic rhinitis treatment satisfaction and preference scale. Allergy Asthma Proc 2013;34:551-7.
56. Baena-Cagnani CE, Canonica GW, Zaky Helal M, Gomez RM, Compalati E, Zernotti ME, et al. The international survey on the management of allergic rhinitis by physicians and patients (ISMAR). World Allergy Organ J 2015;8:10.
57. Demoly P, Aubier M, de Blay F, Wessel F, Clerson P, Maigret P. Evaluation of patients' expectations and benefits in the treatment of allergic rhinitis with a new tool: the patient benefit index—the benefica study. Allergy Asthma Clin Immunol 2015;11:8.
58. Fromer LM, Blaiss MS, Jacob-Nara JA, Long RM, Mannion KM, Lauersen LA. Current Allergic Rhinitis Experiences Survey (CARES): consumers' awareness, attitudes and practices. Allergy Asthma Proc 2014;35:307-15.
59. Zicari AM, Indinnimeo L, De Castro G, Incorvaia C, Frati F, Dell'Albani I, et al. A survey on features of allergic rhinitis in children. Curr Med Res Opin 2013;29: 415-20.
60. Demoly P, Chiriac AM, Berge B, Rostin M. Reasons for prescribing second generation antihistamines to treat allergic rhinitis in real-life conditions and patient response. Allergy Asthma Clin Immunol 2014;10:29.
61. Virchow JC, Kay S, Demoly P, Mullol J, Canonica W, Higgins V. Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients—an observational, cross sectional study in four countries in Europe. J Med Econ 2011;14:305-14.
62. Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of allergic rhinitis symptoms on quality of life in primary care. Int Arch Allergy Immunol 2013;160:393-400.
63. Valovirta E, Myrseth SE, Palkonen S. The voice of the patients: allergic rhinitis is not a trivial disease. Curr Opin Allergy Clin Immunol 2008;8:1-9.
64. Hellings PW, Dobbels F, Denhaerynck K, Piessens M, Ceuppens JL, De Geest S. Explorative study on patient's perceived knowledge level, expectations, preferences and fear of side effects for treatment for allergic rhinitis. Clin Transl Allergy 2012;2:9.

65. Green RJ, Davis G, Price D. Concerns of patients with allergic rhinitis: the Allergic Rhinitis Care Programme in South Africa. Prim Care Respir J 2007; 16:299-303.
66. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, et al. Unmet needs in severe chronic upper airway disease (SCUAD). J Allergy Clin Immunol 2009;124:428-33.
67. Hellings PW, Fokkens WJ, Akdis C, Bachert C, Cingi C, Dietz de Loos D, et al. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? Allergy 2013;68:1-7.
68. Mullol J, Bartra J, del Cuvillo A, Izquierdo I, Munoz-Cano R, Valero A. Specialist-based treatment reduces the severity of allergic rhinitis. Clin Exp Allergy 2013;43:723-9.

RATIONALE FOR USING A VAS IN THE ALGORITHM

Certain differences between groups in their VAS scores or changes in scores might have no clinical relevance, even if they achieve statistical significance. A wide range of minimal clinically important differences (MCIDs) in change scores on the pain VAS have been reported[E1] by using different methods. MCDIs ranged from 9 to 30 mm (of 100 mm) in emergency departments.[E2-E6] In other settings, changes of 33%[E7] and 31 mm[E8] have been shown to be clinically meaningful. In patients with endometriosis, the pain MCID was set at 10 mm.[E9] The MCID for the fatigue VAS was around 10 mm in a large rheumatoid arthritis clinical practice and similar to that seen in clinical trials.[E10] The MCID in the VAS pain score does not differ with sex, age, and cause-of-pain groups[E3] or with the severity of pain being experienced.[E11] However, the linearity of the pain VAS is found in some[E12] but not all[E1,E13,E14] studies. Pain VAS measurement error has been reported to be up to 20 mm.[E15,E16] Consequently, change scores and the calculations of aspects, such as MCIDs, can be carefully considered by the potential lack of interval scaling of the VAS and further compromised by the magnitude of measurement error. Repeated pain VAS data meet the strict requirements of the Rasch model, including unidimensionality, and they were internally valid.[E1] However, the pain VAS does not behave linearly, and the MCID can underestimate or overestimate true change during repeated pain VAS.[E17]

In patients with AR, to our knowledge, there is a single study that has estimated MCDIs in the VAS during treatment.[E18] By using receiver operating characteristic curve analysis, an appropriate method for estimation of MCDIs, the established cutoff variation of 23 mm for the VAS was associated with a cutoff variation of 0.5 for the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Sensitivity analysis with RQLQ and Total Symptom Score 6 scales confirmed the aptitude of the cutoff value (23 mm) to discriminate changes in symptoms and QOL. The MCID was the same whatever the baseline VAS level.[E18] A level of more than 23 mm appears to be a relevant cutoff. VAS changes appear to encompass both symptoms and disease-specific QOL.[E18,E19] Another study, the Control of Allergic Rhinitis and Asthma Test,[E20,E21] approximated the VAS MCDI. In CARAT, the MCID is 4 (range, 0-30).[E22] The real-life study of Demoly et al[E18] in primary care used the same methods as a cluster randomized trial carried out in specialist practices.[E23] Both studies, which were carried out in France in large populations, showed a very similar change in VAS levels during treatment depending on total symptom scores and RQLQ sores. These studies suggest that the cutoff of 23 mm[E18] is appropriate to find a clinically significant difference.

VAS levels appear to be similar in different countries in patients with severe intermittent or persistent rhinitis. A VAS can be used in all age groups, including preschool children (guardian evaluation)[E24] and the elderly.[E25] Furthermore, it can be used in a wide variety of languages.[E25-E32] VAS levels vary with the Allergic Rhinitis and its Impact on Asthma classification in many languages.[E28,E33-E35] A VAS level of 50 (>100 mm) is suggestive of moderate-to-severe AR,[E19,E36,E37] although in some studies the cutoff was greater than 60 mm.[E29] A VAS was used to define severe chronic upper airway disease.[E23] Thus the MCDI found in 2 large French populations can be generalized to other countries with different languages and cultures across the lifecycle. However, future studies should refine this cutoff level.

REFERENCES

E1. Kersten P, White PJ, Tennant A. Is the pain visual analogue scale linear and responsive to change? An exploration using Rasch analysis. PLoS One 2014;9:e99485.
E2. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med 1996;27:485-9.
E3. Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med 1998;5:1086-90.
E4. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med 2001;38:633-8.
E5. Gallagher EJ, Bijur PE, Latimer C, Silver W. Reliability and validity of a visual analog scale for acute abdominal pain in the ED. Am J Emerg Med 2002;20:287-90.
E6. Lee JS, Hobden E, Stiell IG, Wells GA. Clinically important change in the visual analog scale after adequate pain control. Acad Emerg Med 2003;10:1128-30.
E7. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 2003;4:407-14.
E8. Auffinger BM, Lall RR, Dahdaleh NS, Wong AP, Lam SK, Koski T, et al. Measuring surgical outcomes in cervical spondylotic myelopathy patients undergoing anterior cervical discectomy and fusion: assessment of minimum clinically important difference. PLoS One 2013;8:e67408.
E9. Bourdel N, Alves J, Pickering G, Ramilo I, Roman H, Canis M. Systematic review of endometriosis pain assessment: how to choose a scale? Hum Reprod Update 2015;21:136-52.
E10. Khanna D, Pope JE, Khanna PP, Maloney M, Samedi N, Norrie D, et al. The minimally important difference for the fatigue visual analog scale in patients with rheumatoid arthritis followed in an academic clinical practice. J Rheumatol 2008;35:2339-43.
E11. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J 2001;18:205-7.
E12. Myles PS, Troedel S, Boquest M, Reeves M. The pain visual analog scale: is it linear or nonlinear? Anesth Analg 1999;89:1517-20.
E13. Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. Ann Emerg Med 2001;38:639-43.
E14. Emshoff R, Bertram S, Emshoff I. Clinically important difference thresholds of the visual analog scale: a conceptual model for identifying meaningful intraindividual changes for pain intensity. Pain 2011;152:2277-82.
E15. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med 2001;8:1153-7.
E16. DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. Anesth Analg 1998;86:102-6.
E17. Kersten P, Kucukdeveci AA, Tennant A. The use of the Visual Analogue Scale (VAS) in rehabilitation outcomes. J Rehabil Med 2012;44:609-10.
E18. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. Clin Exp Allergy 2013;43:881-8.
E19. Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of allergic rhinitis symptoms on quality of life in primary care. Int Arch Allergy Immunol 2013;160:393-400.
E20. Bousquet PJ, Combescure C, Klossek JM, Daures JP, Bousquet J. Change in visual analog scale score in a pragmatic randomized cluster trial of allergic rhinitis. J Allergy Clin Immunol 2009;123:1349-54.
E21. Azevedo P, Correia de Sousa J, Bousquet J, Bugalho-Almeida A, Del Giacco SR, Demoly P, et al. Control of Allergic Rhinitis and Asthma Test (CARAT): dissemination and applications in primary care. Prim Care Respir J 2013;22:112-6.
E22. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Azevedo L, Sa-Sousa A, Branco-Ferreira M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. Allergy 2010;65:1042-8.
E23. Bousquet PJ, Bachert C, Canonica GW, Casale TB, Mullol J, Klossek JM, et al. Uncontrolled allergic rhinitis during treatment and its impact on quality of life: a cluster randomized trial. J Allergy Clin Immunol 2010;126:666-8, e1-5.
E24. van der Leeuw S, van der Molen T, Dekhuijzen PN, Fonseca JA, van Gemert FA, Gerth van Wijk R, et al. The minimal clinically important difference of the control of allergic rhinitis and asthma test (CARAT): cross-cultural validation and relation with pollen counts. NPJ Prim Care Respir Med 2015;25:14107.

E25. Klimek L, Bachert C, Mösges R, Munzel U, Price D, Virchow JC, et al. Effectiveness of MP29-02 for the treatment of allergic rhinitis in real-life: results from a noninterventional study. Allergy Asthma Proc 2015; 36:40-7.

E26. Morais-Almeida M, Santos N, Pereira AM, Branco-Ferreira M, Nunes C, Bousquet J, et al. Prevalence and classification of rhinitis in preschool children in Portugal: a nationwide study. Allergy 2013;68:1278-88.

E27. Morais-Almeida M, Pite H, Pereira AM, Todo-Bom A, Nunes C, Bousquet J, et al. Prevalence and classification of rhinitis in the elderly: a nationwide survey in Portugal. Allergy 2013;68:1150-7.

E28. Bousquet J, Bachert C, Canonica GW, Mullol J, Van Cauwenberge P, Bindslev Jensen C, et al. Efficacy of desloratadine in intermittent allergic rhinitis: a GA(2)LEN study. Allergy 2009;64:1516-23.

E29. Bousquet J, Bachert C, Canonica GW, Mullol J, Van Cauwenberge P, Jensen CB, et al. Efficacy of desloratadine in persistent allergic rhinitis—a GA(2)LEN study. Int Arch Allergy Immunol 2010;153:395-402.

E30. Ohta K, Bousquet PJ, Aizawa H, Akiyama K, Adachi M, Ichinose M, et al. Prevalence and impact of rhinitis in asthma. SACRA, a cross-sectional nation-wide study in Japan. Allergy 2011;66:1287-95.

E31. Larenas-Linnemann D, Dinger H, Shah-Hosseini K, Michels A, Mosges R. Over diagnosis of persistent allergic rhinitis in perennial allergic rhinitis patients: a nationwide study in Mexico. Am J Rhinol Allergy 2013;27: 495-501.

E32. Shao J, Cui YX, Zheng YF, Peng HF, Zheng ZL, Chen JY, et al. Efficacy and safety of sublingual immunotherapy in children aged 3-13 years with allergic rhinitis. Am J Rhinol Allergy 2014;28:131-9.

E33. Wei H, Zhang Y, Shi L, Zhang J, Xia Y, Zang J, et al. Higher dosage of HIFU treatment may lead to higher and longer efficacy for moderate to severe perennial allergic rhinitis. Int J Med Sci 2013;10:1914-20.

E34. Tatar EC, Surenoglu UA, Saylam G, Isik E, Ozdek A, Korkmaz H. Is there any correlation between the results of skin-prick test and the severity of symptoms in allergic rhinitis? Am J Rhinol Allergy 2012;26:e37-9.

E35. Bousquet PJ, Bousquet-Rouanet L, Co Minh HB, Urbinelli R, Allaert FA, Demoly P. ARIA (Allergic Rhinitis and Its Impact on Asthma) classification of allergic rhinitis severity in clinical practice in France. Int Arch Allergy Immunol 2007;143:163-9.

E36. del Cuvillo A, Montoro J, Bartra J, Valero A, Ferrer M, Jauregui I, et al. Validation of ARIA duration and severity classifications in Spanish allergic rhinitis patients—the ADRIAL cohort study. Rhinology 2010;48:201-5.

E37. Rouve S, Didier A, Demoly P, Jankowsky R, Klossek JM, Anessi-Maesano I. Numeric score and visual analog scale in assessing seasonal allergic rhinitis severity. Rhinology 2010;48:285-91.